REMARKS/ARGUMENTS

By the present amendment, claims 1, 4, 6 and 12 have been amended and claims 2-3, 11 and 14-26 have been deleted rendering claims 1, 4-10 and 12-13 pending in the application. Support for amended claim 1 can be found in previous claims 2, 3 and 11 as well as in the application as filed on page 7, lines 8-10 and page 8, lines 18-28. Claim 6 has been amended to further clarify the claim. The support for amended claim 12 can be found in the application as filed on page 6, line 31 to page 7, line 1. The amendments to the claims have been made without prejudice and without acquiescing to any of the Examiner's objections. Applicant reserves the right to pursue any of the deleted subject matter in a further continuation, continuation-in-part or divisional application. The amendment does not contain new matter and its entry is respectfully requested.

The Official Action dated April 22, 2003 has been carefully considered. It is believed that the amended claims submitted herewith and the following comments represent a complete response to the Examiner's rejections and place the present application in condition for allowance. Reconsideration is respectfully requested.

Election/Restriction

Claims 14-26 have been deleted as being directed to a non-elected invention.

Drawings

We are submitting new Figures 1A-G, 3A-H, 4A-F and 5A-F in order to respond to the Notice of Draftperson's Patent Drawing Review. Figures 1, 3, 4 and 5 have been amended to label the views separately. No new matter is contained in the drawings.

Specification

The Examiner has objected to the specification because there is no description of Figure 5B. In response, page 5 has been amended in order to indicate the reference to Figure 5B.

Claim Objections

The Examiner has objected to claim 4 in view of the phrase "wherein the reporter gene encodes an enhancer element". In response, claim 4 has been amended to specify that the reporter gene comprises an enhancer element.

35 USC §112

The Examiner has objected to claims 8 and 9 under 35 USC §112, first paragraph and requests that a deposit is made of the plasmid "pGL3(4X48)-enhanced green fluorescent protein". We respectfully submit that a deposit is not required as one of ordinary skill in the art could readily prepare the claimed plasmid without undue experimentation. In particular, Applicant first prepared the pGL3(4X48)-luciferase plasmid by subcloning the Sox9 responsive reporter gene 4X48-p89 luciferase (fully described in reference 14) into the commercially available plasmid pGL3 (available from Promega) as described in the application on page 17. To prepare the enhanced green fluorescent protein construct, the luciferase gene was replaced in pGL3(4X48) by cutting this plasmid with HindIII and Xba1 to liberate the luciferase gene and this was replaced with a HindIII-Xba1 fragment containing the EGFP gene from pEGFP-N1 vector. One of skill in the art could readily prepare such a plasmid, especially with reference to the present disclosure.

In view of the foregoing, we respectfully request that the Examiner withdraws his requirements that the "pGL3(4X48)-enhanced green fluorescent protein" plasmid be deposited.

The Examiner has objected to claim 1 as being vague and indefinite. In response, claim 1 has been amended in order to relate the reporter gene to the determination of chondroblast or chondrocyte differentiation and to further define the "determining" step.

The Examiner has objected to claims 8 and 9 which depend from claim 6 and requested that claim 6 be amended to state "further comprising a marker gene". In response, claim 6 has been amended in order to specify that the nucleic acid construct further comprises a promoter and a detectable marker.

The Examiner has objected to the term "at high density" in claim 12. In response, claim 12 has been amended in order to specify that the cells "form a confluent monolayer with precartilaginous condensations evident within 24 hours" which is described in the specification on page 6, line 31 to page 7, line 1.

In view of the foregoing, we respectfully request that all of the objections to the claims under 35 USC §112, first paragraph be withdrawn.

35 USC §102

The Examiner has objected to claims 1, 2, 4-8, 11 and 13 under 35 USC §102(b) as being anticipated by LeFebvre et al. (Matrix Biol.) or LeFebvre et al. (EMBO J.). The Examiner has also objected to claims 1, 2, 4 and 11-13 under 35 USC §102(b) as being anticipated by Nonaka et al. and claims 1, 2, 4-6, 11 and 13 under 35 USC §102(b) as being anticipated by Xie et al.

It is noted that claim 3, that specifies that the cells used in the assay are limb mesenchymal cells, is not included in any of the Examiner's objections. As claim 1 has now been amended in order to incorporate the subject matter of previous claim 3, the claims are novel in view of the cited references. Claim 1 has also been amended in order to specify that the reporter gene comprises a sequence that binds to an endogenous protein (e.g. Sox9) in the cells that is changed upon chondroblast or chondrocyte differentiation. In all of the references cited by the Examiner, Sox9 is produced through the introduction of an expression plasmid encoding Sox9. Therefore, the prior art methods detect exogenously introduced Sox9 using Sox9-responsive

reporters while the present invention uses the Sox9-responsive promoter to follow levels of endogenous Sox9.

In view of the foregoing, we respectfully request that the all of the objections to the claims under 35 USC §102(b) be withdrawn.

35 USC §103

The Examiner has objected to claims 1-8 and 11-13 under 35 USC §103(a) as being unpatentable over each of LeFebvre et al. (Matrix Biol.) or LeFebvre et al. (EMBO J.) in view of Healy et al. We respectfully disagree with the Examiner for the reasons that follow.

By the present amendment, the claims have been amended in order to specify that the cells used in the assay are primary limb mesenchymal cells and that the reporter gene contains a sequence that binds to an endogenous protein in the cells. None of the art cited by the Examiner discloses or suggests an assay for identifying modulators of chondrogenesis containing these elements. The inventors have shown that using primary limb mesenchymal cells is far more advantageous than using other cell types or clonal cell lines. In this regard, we are enclosing an article by the inventors that appeared in the Journal of Cell Science, 116, 2885-2893 in 2003. In the article, the inventors demonstrate that an assay that comprises the primary limb mesenchymal provides a much better model system as compared to using clonal populations of cells such as C2C12 and G8 cells. In fact, the results obtained by the inventors using the primary limb mesenchymal cells were the exact opposite of the results obtained using the clonal cell lines, likely due to the fact that the primary limb mesenchymal cells provide a more accurate *in vitro* model system to study chondrogenesis. Therefore, using primary limb mesenchymal cells offers a clear and unexpected advantage over the prior art systems.

Another advantage to using the primary mesenchymal limb cells is that these cells progress very quickly from chondroprogenitor to a chondroblast (2-3 days) thereby allowing the use of transient transfection rather than transfecting with retroviral or adenoviral vectors which are time consuming to generate. An assay that allows transient transfection is more amenable to high throughput screening and therefore more advantageous in a screening assay.

In view of the foregoing, we respectfully request that the objections to the claims under 35 USC §103(a) be withdrawn.

The Commissioner is hereby authorized to charge any fee (including any claim fee) which may be required to our Deposit Account No. 02-2095.

In view of the foregoing comments and amendments, we respectfully submit that the application is in order for allowance and early indication of that effect is respectfully requested. Should the Examiner deem it beneficial to discuss the application in greater detail, he is kindly requested to contact the undersigned by telephone at (416) 957-1682 at his convenience.

Respectfully submitted,

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Attachments